Management of Branch Retinal Vein Occlusion

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65 year Old Doctor, with no system risk factors.
First presented in Nov 2007 with defective vision in lower field of the left eye

Visual Acuity RE 6/9, LE 6/6, NV with present glass N6, N8 and intraocular tension of 19 Right Eye and 21 Left Eye.

Fig 1. (a) Fundus appearance at presentation showing a non-ischemic BRVO in the left eye. (b) FFA showing a well perfused non ischemic BRVO left eye

Fig 2. Fundus photograph taken after 2 months showing increase in retinal hemorrhages with macular hemorrhages and edema.

Fig 3. (a) OCT 4 months after presentation showing macular edema with a central retinal thickness of 550 mm and subfoveal serous retinal detachment (b) Fundus picture and FFA taken 4 months after presentation showing ischemic conversion with neovascularisation of optic disc and large areas of capillary non perfusion.

Fig 4. Fundus picture at 8 weeks post sectoral laser photocoagulation showing some amount of resolution of macular edema
Fundus Picture (Fig. 1a) and fluorescein angiography suggestive of non-ischemic (BRVO) branch retinal vein (Fig. 1b) occlusion.

The patient was managed conservatively for 6 months with resolution of hemorrhage. On review after 2 months the patient complained of defective vision in his left eye. Ocular examination revealed a visual acuity of 6/18 N\textsuperscript{18} IG and NIP in the left eye. Fundus examination (Fig. 2) showed and increase in retinal hemorrhages with macular hemorrhages and edema. Conservative treatment was continued and the patient reviewed again after 3 months. Review on 4/2008 showed central retinal thickness of 550 microns with subfoveal serous RD (Fig. 3a)

In view of the large areas of capillary non perfusion (Fig. 3b) and worsening of the macular edema sector laser photocoagulation was performed along with focal laser treatment. The patient reported for review on 6/2008.

Vision had deteriorated 6/24 N\textsuperscript{24} in the left eye.

Fundus examination showed worsening of oedema at the macula (Fig. 4)

Your opinion pertaining to the following issues is solicited.

Dr. P. Mahesh Shanmugam

1. What will be your line of management?

This is a 55 year old gentleman who presented with early, partial, superotemporal branch retinal vein occlusion in his left eye that has progressed to a more severe occlusion with loss of vision and neovascularization and ischemic maculopathy ultimately. No pertaining systemic history is available.

Fundus picture at initial presentation shows superotemporal branch retinal vein occlusion with macular edema. Though the patient’s distant vision is 6/6, near vision is N\textsuperscript{8} and an OCT would have been preferable and would allow one to quantify the macular edema – subtle worsening of the macular edema on follow-up will prompt one to intervene.

It is important at this stage to look for the causative disease – based on the fundus pictures and clinical history provided there are two possible causes. There are definite arteriosclerotic changes in both eyes hinting at the possibility of systemic hypertension. The intraocular pressure is at the upper level of normal.

I would have evaluated the patient for systemic hypertension and glaucoma and also for diabetes mellitus. I would not have suggested any active intervention other than control of systemic disease if any and to treat him with anti-glaucoma medication if proved to have glaucoma. I would have reviewed him in 3-4 weeks.

As indicated in the case report, I would have also treated the patient with sectorial scatter laser once the neovascularization is documented, along with macular laser photocoagulation.

The patient continues to have persistent macular edema 2 months after laser photocoagulation with some resolution of the hard exudates. I would suggest a fluorescein angiogram at this stage to look for areas of focal leakage and treat them with focal laser or with grid laser if there is leakage of indeterminate origin. Macular edema may persist because of peripheral ischemia (as seen by the persistent NVD in the fundus photograph) and further fill-in laser photocoagulation of peripheral avascular retina is necessary.

If the macular edema persists 3-4 months after a good grid and focal laser photocoagulation, I would consider anti-VEGF injection.

2. Your schedule for follow up of a patient with vein occlusion.

As this patient has good vision and early, partial branch retinal vein occlusion, I would have reviewed him in 3-4 weeks time to look for subtle progression of the disease such as increased edema on OCT, loss of vision, increasing retinal hemorrhages etc., The signs of progression will prompt me to treat the patient at the earliest. I would also advice the patient to self-evaluate his vision using the newspaper and an Amsler chart and to report earlier than the scheduled appointment if he notices loss of vision.

3. Investigations

Ocular investigations: Other than color fundus photograph, an OCT is necessary. In this patient relevant investigation to rule out glaucoma is also necessary. Fundus fluorescein angiography after resolution of the hemorrhages to look for
macular ischemia, source of macular edema and neovascularization is advisable.

Systemic investigations should include evaluation of blood pressure and diabetes mellitus. If either of these is positive, further investigation is usually not necessary in an elderly patient. A basic work-up that includes complete blood count, erythrocyte sedimentation rate, hemoglobin and peripheral smear is necessary. If the systemic diseases are under good control and the patient experiences repeated attacks of branch retinal vein occlusion,

a. serum homocysteine levels
b. cardiac evaluation (includes examination by a physician, electrocardiogram, echocardiogram and carotid doppler examination)

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c. protein C, S, anti-thrombin, ANA and other investigations are necessary to rule out rare causes in young patients with vein occlusion. These are most often not necessary in the elderly.

4. When do you initiate laser treatment?

I would initiate sectorial scatter photocoagulation with onset of proliferative disease as in this patient or grid / focal laser treatment of macular edema, in persisting macular edema after clearance of hemorrhages (usually 4-6 months after the occurrence of the vein occlusion).

5. Role of intravitreal Pharmacotherapy

I do prefer intravitreal pharmacotherapy in the acute stage of the vein occlusion in an attempt to restore the edematous macula to its original anatomy at the earliest to decrease the chances of irreversible intrinsic damage. My choice of pharmacotherapy is with anti-VEGF agents after ensuring that the patient is not at an increased risk for thromboembolic disease. A cut-off vision such as less than 6/18 Snellen vision or documented progression of the disease can be used to initiate treatment. An OCT provides necessary evidence of progression of the disease by documenting worsening macular edema.

6. Role of combination therapy

After keeping the macula dry with the aid of anti-VEGF agents, I would consider macular photocoagulation once the macular hemorrhages clear, as combination treatment is likely to reduce the need for repeated anti-VEGF injections. A peripheral sectorial laser photocoagulation may be considered in patients with persistent or recurrent macular edema – in these patients the peripheral ischemia may be stimulus responsible for persistent macular edema.

Dr. Gopal S Pillai

1. What will be your line of management?

The clinical pictures and fluorescein angiographic pictures as of November 2007 clearly depicts a typical nonischemic suprotemporal branch retinal vein occlusion. There are also changes of arteriosclerosis (Shie’s classification stage III) in both eyes. We can also see the artery cross over the vein and compressing the vein in one location. However with vision of 6/6, N6, our management would be conservative, as was done in this case. We would also get an OCT through the macula to look for evidence of CME. Even with 6/6 vision, there may be CME on OCT, even though that would not have made a difference in our management as the vision was unaffected. Anyway, that would have allowed us to document the presence or absence of CME. BRVO study has been the only randomized clinical trial in the management of BRVO and it has clearly defined the management aspects of BRVO. The final end result in observed and favorable cases were better than 6/12 in a majority of patients. I personally do not hesitate to deviate from the BRVO study recommendations in cases where I feel that the end result can be better than 6/12 with modern management modalities.

2. Your schedule for follow up of a patient with vein occlusion

BRVO patients are followed up monthly for the initial 3 months and there after if there is improvement, then, I would follow up 2 monthly for the next 6 months. After that we may maintain a 6 monthly follow up. Each visit, we would look for vision, IOP, anterior segment and iris examination, resolution of hemorrhages, increase or decrease of edema or appearance of neovascularisation. If the patient is improving, we may consider laxing of the follow up schedule. If there is a worsening from one visit to the next, we may consider FFA and OCT and then treatment depending on the same.

3. Investigations

This patient is 65 years and has arteriosclerotic retinopathy also. He is in a typical risk group of
developing BRVO. Hence, we would get a general medical consult with blood pressure, lipid profile and other basic investigations and if anything is found positive, we will emphasize the need for its treatment for the resolution of the eye condition. If we are dealing with a young patient with BRVO, then we may consider other investigations also like peripheral blood smear and blood picture, coagulation studies, protein s and protein c, homocystine levels and anti cardiolipin factor. Some patients with long standing hypertension may have to be investigated for end organ damages due to hypertension as advised by the physician. We should actively discuss with the patient that the retinal vessel block is just an indication that many vessels in the body may be defective because of the underlying systemic disease.

4. When do you initiate laser treatment?

Scatter laser treatment is planned when there is neovascularisation or extensive areas of ischemia. In cases with CME we may consider focal laser if it is associated with areas of ischemia. We would also ablate the areas of ischemia along with the focal laser if they are large areas.

5. Role of intravitreal Pharmacotherapy.

When there is significant CME, our initial management was focal macular laser up till 5 years back, but as of now, in significant CME, in cases with good perfusion, we treat the patient with an anti VEGF injection and wait for the edema to come down. In most such cases, there is a significant increase in vision and reduction of macular edema and if there is recurrence of CME we may consider re injection for the patient. We have found in personal experience that a single re injection is needed in about 40 % of patients and more than 1 re injection in 15 % of cases. We have also seen that ranibizumab has a stronger ability to flatten the retina and improve vision than bevacizumab (nonrandomized study). We feel that if the edema is high, then there is no need to wait as waiting will cause anatomical changes in the fovea and thereby reduce the visual prognosis in such cases.

Triamcinolone acetonide also has good results in the management of BRVO. However the chances of glaucoma is more in cases with vascular block as many patients may be predisposed and so steroid responders.

In cases where anit VEGF is contraindicated, we may consider IVTA or a posterior subtenons kenacort.

But in cases with ischemia, we would be very conservative with anti VEGF injections and may follow the BRVO study recommendations on laser. This is because there are some reports of anti VEGF agents increasing the ischemia.

The basic idea is that in cases with good prognosis, defended by BRVO study as an end result better than 6/12, we want to raise the bar from 6/12 to near about 6/6 as the end result with the newer pharmacotherpies available to us.

6. Role of combination therapy.

In recurrent macular edemas in well perfused retinas, which require more than 1 reinjection, we would plan a focal macular laser after anti VEGF injections. If large areas of ischemia are present, then we would be more comfortable ablating the large areas of ischemia with scatter laser. In neovascularisations, which are very large, I use combination therapy with anti VEGF followed by scatter laser.

Additional comments on this case

In this case, worsening of vision was probably due to increasing ischemia due to progressive block of the vessel. This could be due to compression of the vein by the artery in the common adventitious sheath as seen in the picture and the FFA. Retrospectively this case may have been a candidate for sheathotomy. (I do not have any personal experience on sheathotomy.)

Dr. Rajesh P

1 When the BRVO is perfused with no macular edema as when the patient presented the first time I would have suggested observation and would have called the patient for follow up after 3 months or asked the patient to report if there was any decrease in vision. Investigations to find out the cause of BRVO also would have been done.

When he presented with worsening of occlusion and drop in vision in Jan 2008, considering that there was not much retinal hemorrhage I would have done a ffa to asess the macular perfusion first. I would also have given an intravitreal agent like triamcinolone or avastin in the first instance even if
FFA had not been possible. In case of minimal edema PST 80 mg would have been another option

The FFA picture in 4/2008 shows extensive foveal ischemia. Ocm shows sub retinal and intraretinal fluid which warrants the use of intravitreal agent like triamcinolone. In the presence of capillary drop out involving almost 2/3 of the perifoveal capillary network I would not have done macular laser. Since there is already accumulation of hard exudates, to prevent further exudate deposition during resolution of edema, lipid lowering drugs could have been prescribed if the lipid levels were above the borderline.

When there is a worsening of edema as in 6/2008 I would have thought about switching to avastin or if there had been an initial resolution with IVTA, repeated the injection. Combined ivta and avastin is also worth a try according to some reports.

2. Follow up often depends on the initial treatment given to the patient. If ivta or pst is given the patients are followed up at 2 weeks intervals for the first month to check the iop. Patients who have received PST may also require repeat injection at 2 -3 weeks. Those who have received intravitreal injections are also advised to report if there is any worsening of vision, increase in pain, photophobia etc to rule out endophthalmitis. If FFA was not possible due to extensive hemorrhage it is done when the hemorrhage has cleared. After one month the patients are followed up at 1 month interval for the next two months. In the mean time decision regarding further treatment –either further injections or LASER is made. These patients are subsequently followed up at 3 monthly intervals or if there is a decrease in vision.

In patients with extensive area of capillary non perfusion chances of neovascularisation of the retina is there and they are followed up at 3-4 month intervals for 1 year and at 6 month intervals for the next 3 years.

3. Glaucoma has to be ruled out. HT, DM AND DYSLIPIDEMIA have to be investigated for. A complete hematological work up including hb, tc, dc, esr, peripheral smear, platelet count ,bt, ct, pt, apt t, may also be done if vascular occlusion cannot be explained by common associations. If clinical features are suggestive, myeloma or other hyper viscosity syndromes also has to be ruled out. In young individuals vasculitis and causes of vasculitis also have to be considered. Serum homocysteine levels and protein c s levels also have to be assessed in young patients. Fluorescein angiography helps to assess foveal perfusion and also the extent of retinal ischemia. Ocm can be of help to quantify the macular edema, presence of CME and any subfoveal fluid and to asses the response to treatment.

4. LASER for macular edema is done only after FFA when retinal hemorrhages have cleared sufficiently and only for perfused macular edema. Laser is the only treatment supported by evidence to be beneficial to these patients. In practice Laser is done for perfused macular edema in patients who have not received any treatment and also for persisting or recurring perfused edema after treatment with intravitreal agents. Some patients can have a natural resolution of the edema in the first three months which may be facilitated by intravitreal agents and hence laser is done only after 3 months. It is done in a grid fashion in the area of capillary leakage with special attention to ablate the leaking micro aneurysms. Collaterals should be avoided at the time of LASER.

Neovascularisation occurs in only 22%of patients with capillary nonperfusion more than 5 DD by 4 years (BVOS data). Scatter laser may cause constriction of the visual field. Also approximately 12% of patients who have received prophylactic scatter laser still develop neovascularisation. Hence Laser for neovascularisation is done only after the patient has developed NVE or NVD. An exception is where the patient is likely to be noncompliant or has difficulty to maintain the follow up.

5. Intravitreal pharmacotherapy for macular edema is initiated as early as possible. This is given even before FFA is possible; to limit the edema induced damage. There are few concerns about anti vegf agents preventing development of collaterals and thus the natural resolution of edema. Hence Ivta is often preferred as the first line of management. In patients with glaucoma, known steroid responders’ avastin is given. Patients receiving intravitreal
therapy can often have recurrence of edema and may require laser or additional injections. It has to be stressed that visual recovery after the treatment is decided by the extent of foveal ischemia.

In neovascularisation with vitreous hemorrhage avastin may help to clear the media and facilitates further laser treatment. The chance for worsening of the tractional component and the need for a subsequent surgery also has to be highlighted. In non resolving vitreous hemorrhage and trd threatening macula avastin can be given intravitreally 1 week before surgery to reduce the bleeding during surgery.

6. Combined treatment for macular edema can be tried when the edema is not severe and when there is not much retinal hemorrhage. Combined laser and ivta has been found to yield better visual outcomes than laser alone. Combined treatment but was found not to have as good visual outcome as ivta alone in another study. No strong evidence is available to support combination treatment and further studies are required. Combination of ivta and avastin is an option available when edema is not responding to other treatment modalities.

Dr. Shane Mathew

Here we are dealing with an elderly gentleman with branch retinal vein occlusion in left eye evolving to an ischemic one which is non responsive to laser photocoagulation showing worsening of edema and visual acuity, with borderline intraocular pressure. First of all it is important to ask for risk factors in the form of hypertension, diabetes mellitus, ischemic heart diseases, history of stroke/thromboembolic events etc and get a systemic evaluation done. In the mean while I would like to check for presence of neovascularisation of iris or and neovascularisation of angle; presence of which may warrant aggressive laser photocoagulation. I feel he is extremely lucky to have 6/24 N24 with this much macular non perfusion. Angiogram done in April 2004 shows evidence suggestive of neovascularisation. During fundus evaluation I would look for skipped areas of photocoagulation, assessing the need for fill in photocoagulation, pressure of epiretinal membranes and type of macular edema. Coming to macular edema an Optical Coherence Tomography at this stage would be ideal to decide on the cause for worsening. If vitreo macular traction is responsible for it, then vitrectomy would be the ideal choice. But for pure edema; at this stage I would prefer to inject Anti VEGF instead of steroids as pressures are in borderline; after explaining to the patient the goal, risks and benefits of treatment, and augment with fill in photocoagulation in the form of sectorial photocoagulation and focal to area of edema may be after a week of injection. (My rationale being that Anti VEGF takes care of VEGF up regulation and thus help in regression of neovascularisation, reducing edema (if not controlled can lead to secondary changes at macula reducing the vision even further.) and photocoagulation taking care of hypoxia which is the primary pathology.) Here I would like to avoid treating over collaterals.

I would like to review the patient after 4 weeks to asses the response. If edema is decreasing one could wait for 2-3 months. If edema is not showing any response I would like to try intra vitreal steroids this time taking into consideration its potential risks.

Combination Therapy could also be called as “Laser plus Therapy”. Laser plus something else! Adjunctive intra vitreal therapy provides several benefits including rapid onset of action especially with Anti VEGF agents and dramatic visual improvements. Patients are visually quiet satisfied. Adding Intravitreal therapy also eliminates initial worsening of vision that might be caused by inception of laser therapy. It is effective in case involving media opacities, it controls neovascularisation and as a pre treatment; may potentially make macular laser safer. At the same time disadvantage of intravitreal therapy may be considered; it is invasive, potentially blinding, effects may be short lived. Further more long-term treatment may impair neuro protection and recurrent cost of treatment may also be an issue.

I would not prefer combination therapy in the form of steroids with Anti VEGF initially in this case, as we all know these agents give only short term benefit and steroids may cause rise in intraocular pressure, and cataract. Failing not to mention that anti VEGF can rarely worsen ischemia.

Dr. Thomas Cherian

1. In view of the worsening of oedema, I would consider injecting a VEGF inhibitor at this point.
Following injection, the OCT will be repeated after 2 weeks, we expect the macular oedema to come down. This will be followed by a repeat FFA, and further Laser, if necessary (either microaneurysms or capillary non perfusion areas).

2. On presentation, I would do an OCT. This is a baseline. I would get the blood sugar, BP and lipid profiles checked and call the patient back with reports. Any variation has to be taken care of. I would call back the patient once in 6 weeks and repeat the OCT. Interference (FFA, injection and / or Laser) will be only after 3 months, unless the patient is hard pressed for time.

3. OCT on presentation. Blood sugar, BP, Lipid profiles. In younger individuals, especially with CRVO, ask for a Serum protein C and Protein S. Carefully, look for signs of vasculitis, do a vasculitis workup, if necessary. OCT is repeated every 6 weeks. If there is no improvement in 3 months, I would consider an FFA. In CRVO, I would get an ERG also done, since this will pick up ischaemia, quite early.

4. I would laser almost all BRVOs, for preventing a possible vitreous hemorrhage in future. For CRVOs, I would laser only if there is NVD OR NVE, since a panretinal photocoagulation might cut off the peripheral vision, which the patient may have. Still, I might not wait for a neovascular glaucoma to develop, as recommended by learned experts (SS Hayreh).

5. In macular oedemas, not resolving in 3 months, I would consider intravitreal injections, preferably Bevacizumab (Avastin). Triamcinolone, if at all, has to be used with caution in vein occlusions, a careful follow up of the IOP should be made in such cases.

Combination therapy for BRVO with macular oedema would be my choice. Any VEGF inhibitor injection, I would follow up with a Laser (Sector photocoagulation). Again, in CRVOs, I would follow up an injection with laser, only if there is NVD / NVE.

Compilation

This 65 year old male patient with no obvious risk factors was under follow up and treatment for a branch retinal vein occlusion is in his left eye. He underwent a baseline systemic work up which included fasting and post prandial blood sugars, serum lipid profile and blood pressure. He also underwent a baseline glaucoma work up which was non contributory. During the course of follow up he developed worsening of visual acuity, ischemic conversion and aggravation of macular edema for which sector laser photocoagulation was initiated. 2 months post laser there was recurrence of macular edema for which he underwent additional fill in sectoral photocoagulation along with intravitreal Bevacizumab 0.05 ml / 1.25 mg injection. There was good resolution of the macular edema and stabilization of visual acuity at 6/18 N₈.

A thorough comprehension of the natural history of retinal venous occlusive disease is required in order to initiate treatment strategies at the earliest. All ocular and systemic risk factors for developing retinal vein occlusion should be addressed. While medical therapies have primarily addressed the sequelae of vein occlusion, surgical therapies have generally focused on anatomically circumventing or resolving the vein occlusion. Current management strategies for Branch retinal vein occlusion is given in table 1

**Current Management Strategies for Vein Occlusion**

| Observation | Grid pattern laser photocoagulation |
| Intravitreal Pharmacotherapy | (Triamcinolone Acetonide / Anti VEGF) |
| Sustained Steroid release devices | Vitrectomy with arterio-venous sheathotomy |

To date Grid Laser photocoagulation is the only advocated treatment modality for non ischemic macular edema in eyes with BRVO. It is prudent to wait until neovascularization is present before initiating scatter laser photocoagulation in eyes with BRVO, although treatment may be initiated in eyes with extensive ischemic disease if following up is questionable.

Intravitreal steroid or anti-VEGF therapy is currently employed for reducing macular edema in BRVO. The potential ocular side effects of steroids and potential systemic effects of anti-VEGF agents should be discussed with the patient and an informed consent obtained before the procedure. Despite widespread use of intravitreal triamcinolone, long-term
data are still awaited. The results of the SCORE study will determine the true efficacy and safety of intravitreal triamcinolone.

In the management of BRVO, medical therapies should be considered before pursuing surgical options. Currently surgical therapy has very few indications. Pars plana vitrectomy with endolaser may be appropriate in eyes with non clearing vitreous hemorrhage. Non randomized studies have shown some benefit of Arteriovenous sheathotomy in re-establishing retinal perfusion, reducing intravitreal hemorrhage, and macular edema and in improving visual acuity. It is thought that decompression of the vein in this manner will allow venous recanalisation and displacement of the thrombus from blockage site with the return of distal circulation.

Combined medical and surgical therapies require more study before inclusion as a standard of care.

The visual outcome of BRVO id generally favorable with 30% having 6/18 or both vision. As shown by the BVOS, grid laser photocoagulation can be used in cases of perfused BRVO with persistent vision loss to treat any macular edema with only moderate visual expectations. Scatter laser PHC is recommended for neovascular sequlæ. After the initial visual acuity assessment, IOP measurement, anterior segment examination, undilated gonioscopy, dilated fundus evaluation and subsequent FFA and OCT can be obtained. Affected patients should be followed monthly for 6 months. And at each visit undilated gonioscopy, IOP measurement and dilated fundus examination is necessary to detect neovascularization. NVG occurs in 40-60% of eyes with non perfusion ³ 10 DD often by 3 months post occlusion.